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EP 0272045 A2 **EP 0271332 A2** **WO 93/20799 A1**

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INT CL[6] **A61K 9/06 9/08 9/10 9/107**
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(54) Supersaturated pharmaceutical compositions

(57) A pharmaceutical composition for topical application comprising
a) a pharmaceutically active agent, and
b) a pharmaceutically acceptable vehicle,
the composition having a pH of 7 to 12 or a pH of 3 to 4,
characterised in that the pharmaceutically active agent is dissolved at or below its saturation concentration and that the composition becomes supersaturated when the pH is changed to between 4.5 to 6.5.

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Figure 3

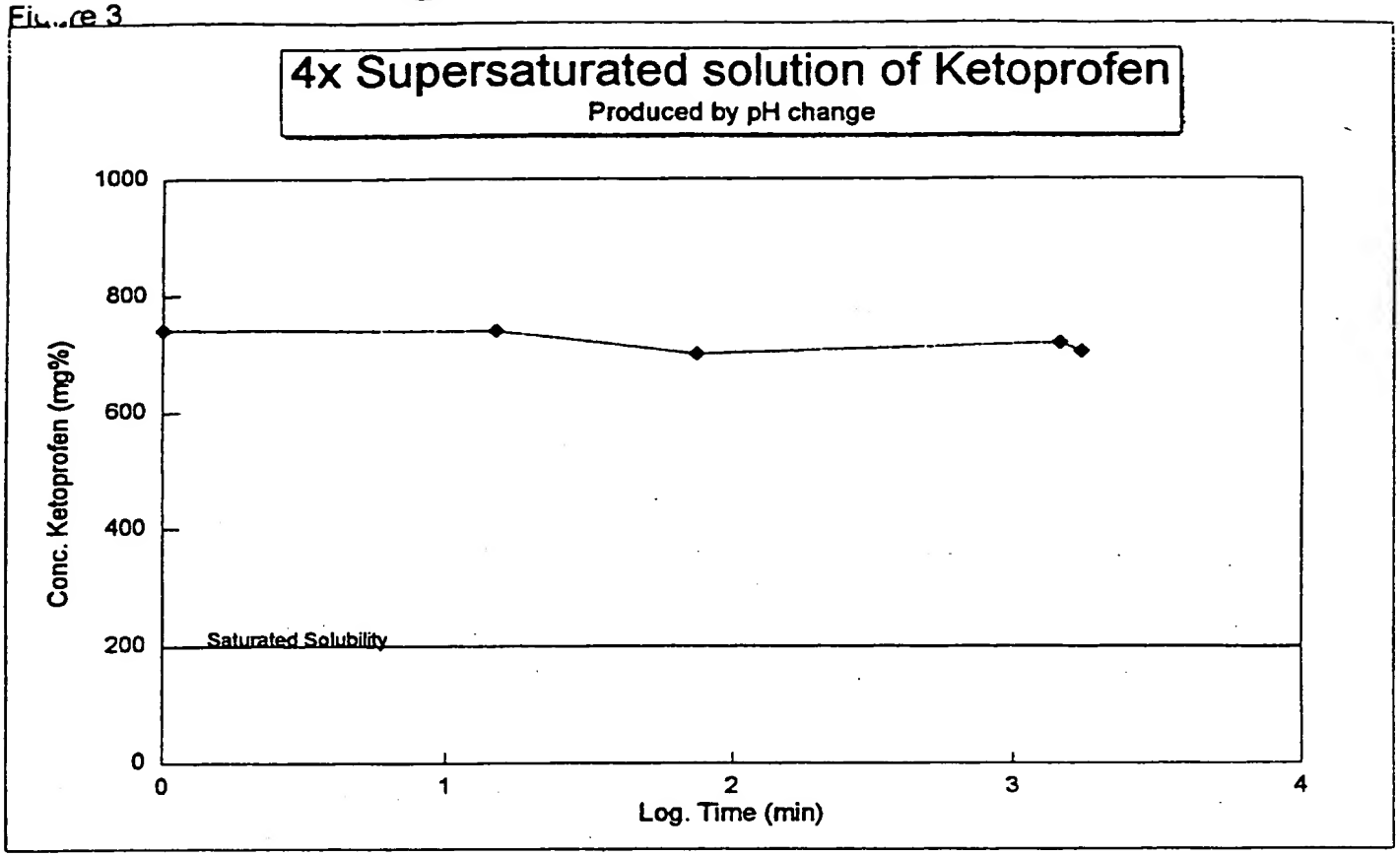
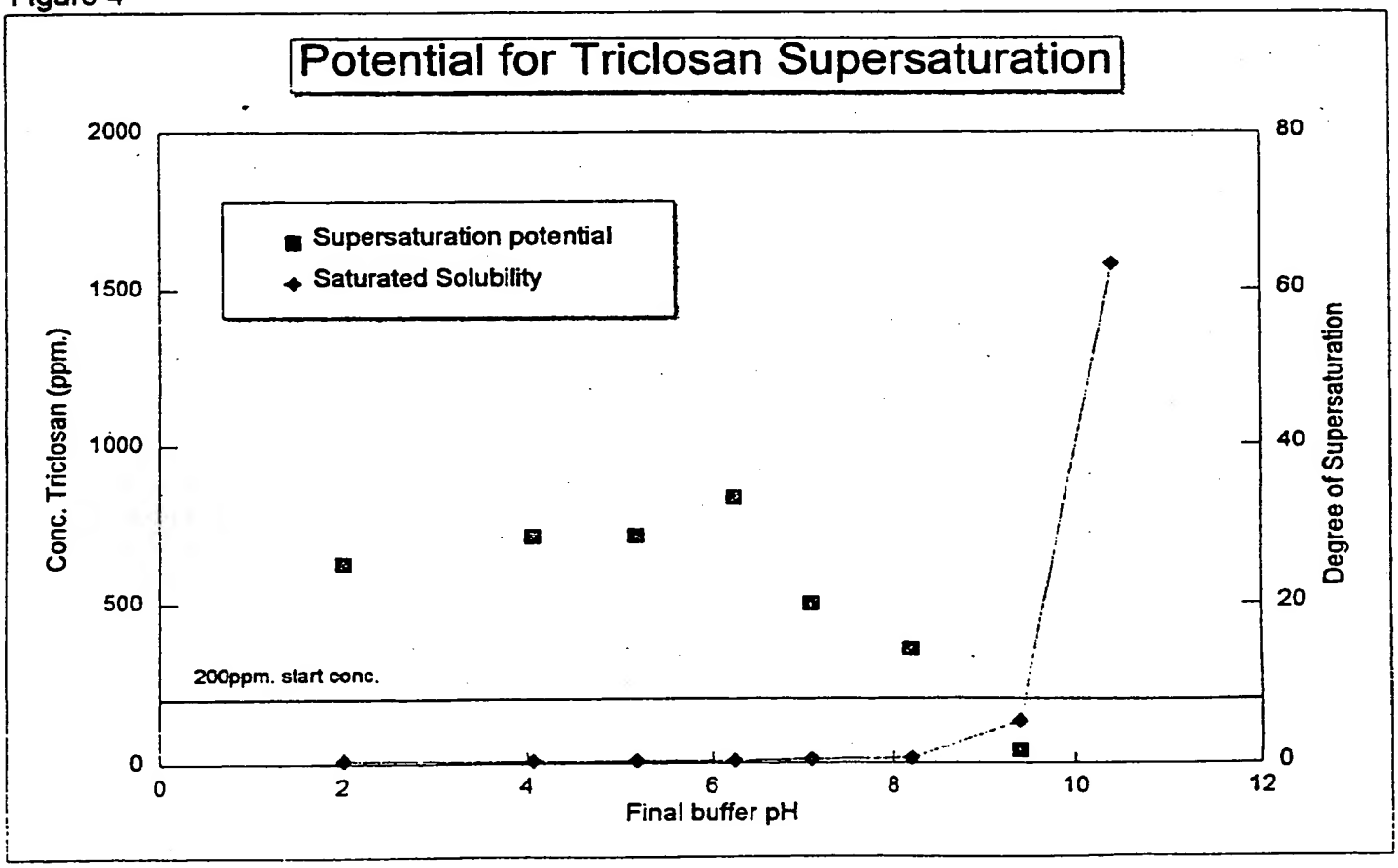


Figure 4



when applied topically, the volatile solvent rapidly evaporates causing the drug concentrate remaining in the non-volatile solvent to increase to a supersaturated level. This increase in drug concentration to supersaturation has been found to increase the rate of drug penetration into the skin.

However, a disadvantage of this system is that the volatile (eg ethanol) causes damage to the skin lipid membrane and may also be taken up by the body. Also, packaging has to be sophisticated enough to prevent evaporation of the volatile - which leads to long term storage difficulties.

Another method to produce supersaturated compositions for the percutaneous penetration of active agents has been to produce a composition for topical application made up of two liquid phases, one containing the drug which has been dissolved in that phase and the other, which may be physically and/or chemically different from the first (but miscible with it), optionally also containing the same drug dissolved therein. The concentration of drug in each phase is such that, on admixture of the phases, the resultant total drug concentration is greater than the saturated drug solubility in the initially formed mixture of

buffer applied liquids to a pH of 4.5 to 6.5 may be sufficient to cause such a solubility change, and therefore produce a supersaturated solution.

There is therefore provided a pharmaceutical composition for topical application comprising

a) a pharmaceutically active agent, and

b) a pharmaceutically acceptable vehicle, the composition having a pH of 7 to 12 or a pH of 3 to 4,

characterised in that the pharmaceutically active agent is dissolved at or below its saturation concentration and that the composition becomes supersaturated when the pH is changed to between 4.5 to 6.5.

Compositions of the above type are suitable to provide active agents to act locally (ie at the site of application) or systemically (ie transdermal application).

Further according to the invention there is provided a method for topical application of an active agent comprising applying to an area of the surface of a body a composition comprising a pharmacologically effective amount of a pharmaceutically active agent dissolved in a pharmaceutically acceptable vehicle, the composition having a pH of 7 to 12 or a pH of 3 to 4 before

The choice of suitable anti-nucleating agent will depend upon the particular active agent and the particular vehicle being used, but suitable anti-nucleating agents can readily be chosen by simple experiment. This may be done, for example, by preparing samples of the desired final supersaturated active agent solution containing a selection of anti-nucleating agents (in say 1% concentration), one to each sample; allowing the samples to stand for, say two hours and noting which solutions have remained clear, and thus stable. Further standard techniques may be used to quantify the effect observed.

A very wide range of active agents and vehicles may be used in the compositions of the invention the only criteria, other than pharmaceutical acceptability, being that the active agent is soluble in the vehicle at a pH within the range of 7 to 12 or 3 to 4 and substantially less soluble in the vehicle at any pH within the range of 4.5 to 6.5.

The degree of improvement in active agent penetration will depend largely upon the ratio of the supersaturated concentration (ie the actual concentration of the active agent in the composition after the pH change on the skin) to the saturation concentration (the

Suitable vehicles for use in the compositions of the invention will be those in which the active agents will be ionisable. More preferably the vehicles will be at least partly aqueous and most preferably they will be predominantly water.

It will be understood that the vehicles used in the compositions of the invention may be mixtures of two or more components as long as all of these components are miscible. Whilst it is most preferred that the vehicles of the compositions of the invention are water they may also be for example mixtures of water and alcohols (eg ethanol or propylene glycol).

Preferred active agents for use in the compositions of the invention are those which are ionised in the pH range of the compositions (ie 3 to 4 or 7 to 12). Furthermore, it is also preferred that the active agents will be substantially unionised at the pH range of the compositions after application to the surface of a body (ie from 4.5 to 6.5).

More preferably the active agents used in the compositions of the invention will be acids with a pKa of 6.5 to 10, bases with a pKa of 4 to 4.5, or amphoteric agents with an acid pKa of 6.5 to 10 and a base pKa of 4 to 4.5

For local applications the following classes of active agents are preferred in the compositions of the invention: antimicrobial agents (eg antibacterial, antifungal or antiviral agents), steroids, antipsoriasis agents, antiacne agents, local anaesthetics, non steroidal anti inflammatory agents, antidandruff agents, headlice treating agents and antihistamines.

Preferred antimicrobial agents include triclosan (preferably 0.01 to 2.5%w/w), hexylresorcinol (preferably 0.05 to 5%w/w), tetracycline (preferably 0.1 to 5%w/w), miconazole (preferably 0.1 to 4%w/w), acyclovir (preferably 0.1 to 5%w/w), metronidazole (preferably 0.01 to 8%w/w), 4-chloro-3-methylphenol (preferably 0.1 to 10%w/w), 4 chloro-3,5-dimethylphenol (preferably 0.1 to 10%w/w) and 2,4-dichloro-3,5-dimethylphenol (preferably 0.1 to 10%w/w).

A preferred steroid is hydrocortisone (preferably 0.1 to 5%w/w).

A preferred antipsoriasis agent is methotrexate (preferably 0.001 to 0.5%w/w).

A preferred antiacne agent is retinoic acid (preferably 0.0001 to 5%w/w).

Preferred analgesics include indomethacin (preferably 0.01 to 1%w/w) and naproxen (preferably 0.1 to 2%w/w)

Preferred anticoagulants include warfarin (preferably 0.001 to 0.1%w/w).

Preferred anti-emetics include metoclopramide (preferably 0.005 to 1.0 w/w).

Preferred antimicrobial agents include triclosan (preferably 0.001 to 1.0 w/w).

Preferred bronchodilators include salbutamol (preferably 0.001 - 0.5% w/w), beclomethasone (preferably 0.001 to 0.05% w/w), ipratropium (preferably 0.0001 to 0.01% w/w).

Preferred antiallergy agents include ketotifen (preferably 0.001 - 0.1% w/w).

Preferred antimigraine agents include clonidine (preferably 0.01 to 1.0% w/w) and ergotamine (preferably 0.0005 to 0.5% w/w).

Preferably compositions according to the invention may further include one or more of the following agents selected from

i) a thickener (preferably a carbomer, e.g. Carbopol 940) - preferably in an amount of 0.1 to 5.0% w/w,

ii) a humectant, preferably selected from glycerol, sorbitol, propylene glycol and tricetin, (more preferably glycerol),

- preferably in an amount of 0.1 to 20% w/w; and

iii) a solubiliser to enhance the solubility of the active agent before application to the surface of a body (preferably propylene glycol) - preferably in an amount of 0.1 to 50% w/w).

Optionally, the composition may contain a penetration enhancer, preferably Azone, or terpenes at a preferred amount of 0.1 to 10% w/w.

Preferably compositions according to the invention contain 30 - 99.5% water.

Preferably the compositions of the invention are free from agents which might act to counter the pH change

The invention will be illustrated by the following examples:

Example 1

Effect of pH on ketoprofen solubility.

Run 1

A range of solutions comprising mixtures of 0.1M citric acid and 0.2M Na_2HPO_4 were produced having the pHs shown in table 1. A weight of ketoprofen, as shown in table 1, was added to a 20ml sample of each solution and the mixture was stirred for 24 hours at 25°C. The pH of the final solution was measured.

Table 1

Original pH	amount of ketoprofen added (g)	pH on sampling after 24 hours
3	0.1	3
4	0.1	4
5	0.1	4.9
5.5	0.5	5.4
6	0.5	5.8
6.5	0.5	6
7	0.5	6.2

Run 3

Saturated solutions of ketoprofen were prepared by a different method to runs 1 and 2 to act as a check on methodology.

4g of ketoprofen was added to 100 ml of deionised water and stirred at 25°C for 24 hours. The pH was tested and found to be 3.5, a sample was taken.

The mixture was then adjusted to a pH of 5.8 with 1M NaOH and stirred for a further 24 hours at 25°C, after which a sample was removed.

The mixture was adjusted to a pH of 6.4 using 1M NaOH and again stirred for 24 hours at a temperature of 25°C. A final sample was removed.

The three samples were filtered to remove undissolved ketoprofen (0.2 um filter) and the concentration of dissolved ketoprofen measured by the same method as in Runs 1 and 2.

The results are shown in figure 1.

Figure 1 demonstrates the vast change in ketoprofen solubility caused by pH changes. Similar results may be

theoretical degrees of supersaturation could be achieved by increasing the starting point pH until still higher ketoprofen solubility is achieved.

The ketoprofen solubility values for the pH 4.9, 5.4, 5.8 and 6.3 shown on figure 2 are averages of the equivalent concentrations from runs 1 and 2. All other values are the same as in Example 1.

Example 3

Stabilisation of a supersaturated solution.

An aqueous solution of 0.8% w/v ketoprofen at a pH of 10.4 was prepared at 25°C. 1% polyvinyl pyrollidone (PVP) was added to the solution. Aliquots of 0.1M hydrochloric acid were added to the solution with stirring until a pH of 5.5 was achieved. A 4X supersaturated solution of ketoprofen was thus produced.

The amount of ketoprofen dissolved in the solution was measured at various times by the method used in Example 1 (after filtration through a 0.2um filter to remove undissolved ketoprofen).

The results are shown in Figure 3, which shows that supersaturation was maintained for at least 16 hours.

Samples of each mixture were centrifuged at 3000 rpm for 10 minutes to remove undissolved material. The concentration of dissolved triclosan was measured in each solution by HPLC using a standard procedure (detection at 281nm).

The solubility of triclosan at each pH is shown in Figure 4.

The supersaturation potential of a solution at pH 10 containing 200ppm triclosan was calculated by dividing the concentration of triclosan in that solution by the concentration of triclosan in the solutions at lower pHs.

These theoretical values are also shown in Figure 4. Thus it can be seen that the degree of supersaturation achievable at a skin pH (eg 5.5) is 30X if a 200ppm triclosan solution at pH 10 is used as the starting composition. It is to be understood that higher degrees of supersaturation may be achieved by increasing the triclosan concentration in solution at pH 10, or further by increasing the pH of the starting composition.

The pH of the formulation is adjusted to ensure a pH of 9. Upon application to the skin, the change in pH of the composition to between 4.5 and 6.5 will result in the formation of an approximately 10X supersaturated composition.

5. A composition as claimed in any preceding Claim further comprising at least one of

a) 0.1 to 5.0% w/w, of a thickener,

b) 0.1 to 20% w/w of a humectant,

c) 0.1 to 50% w/w of a solubiliser, or

d) 0.1 to 10% w/w of a penetration enhancer.

6. A pharmaceutical composition for topical application as hereinbefore described with reference to Examples 5 and 6.